PETITION FOR PARTIAL EXEMPTION FROM SPECIAL PACKAGING REQUIREMENT

AUGUST 14, 2000

PP00-1

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No Comments made
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PP-00-1

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2000 AUG 14 P 4:30
OFFICE OF THE SECRETARY
CPSC

Office of the Secretary
Consumer Product Safety Commission
4330 East-West Highway
Room 502
Bethesda, Maryland 20814

PETITION FOR PARTIAL EXEMPTION FROM SPECIAL PACKAGING REQUIREMENT

Pursuant to Part 1702 of the Commission's regulations at 16 C F.R., and on behalf of Endo Pharmaceuticals, Inc ("Endo"), Chadds Ford, Pennsylvania, the undersigned file this petition for a partial exemption from the special packaging requirements the Commission seeks to enforce against Endo's prescription drug product, Lidoderm® (lidocaine patch 5%). The justification for the partial exemption is that it is not practicable to market each Lidoderm® patch in a child-resistant envelope, as the Commission staff have requested.

I. LIDODERM®

A Product and Packaging Description

Lidoderm® is comprised of an adhesive material attached to a [redacted] film release liner The release liner is removed prior to applying the adhesive side of the patch to the area of the body to be treated

Lidoderm® is a unique patch. The active ingredient, 700 mg of lidocaine (50 mg per gram of adhesive), is uniformly blended with the adhesive on the patch This means that, unlike other patch drug products, Lidoderm® does not have a reservoir of active drug substance Therefore, manipulation or cutting of the patch will not affect the release profile of lidocaine. This proprietary system is unique in the United States and no other legend pharmaceutical patch is produced in this manner Other patches may have reservoirs or matrixes that contain the active ingredient. These systems may release all of the active ingredient if damaged.

When Lidoderm® is applied directly over the affected area, low doses of lidocaine diffuse slowly from the adhesive layer and into the epidermal and dermal layers of the skin Three Lidoderm® patches will give a peak plasma level of 0 13 µg/mL A blood level over 3 µg/mL is required for analgesia. The suggested mechanism of action of Lidoderm® is the blockage of sodium channels in damaged nerve fibers Lidoderm® will cause a reduction of pain (analgesia) without significant numbness (anesthesia). This is in direct contrast to the EMLA® lidocaine patch and topical lidocaine products which, if used for postherpetic neuralgia, would cause anesthesia, not analgesia

The Lidoderm® patch is a 22 square inch patch (10 cm x 14 cm) This is substantially larger than most patches in the U S market For comparison, the Catapres® (clonidine) patch is 0 6 square inches, the Nicoderm® (nicotine) patch is 1 6 square inches, the Duragesic® (fentanyl) patch is 3 4 square inches, and the EMLA® (lidocaine) patch is 6 25 square inches Lidoderm® also differs in that it is very pliable so as to conform to the contours of the part of the body to which it is applied

Lidoderm® is supplied in the form of five patches inside a resealable foil envelope The foil envelope must be resealable to maintain the integrity of the product, as no more than three patches are recommended for use within a 24-hour period, and there are five patches in each envelope. Six envelopes are contained in one carton. The specifications for the patch, the envelope, and the box are included as Attachment 1. One sample of the product as packaged (i e., carton with six envelopes inside) is included as Attachment 2.

Lidoderm® is manufactured in Japan by Teikoku Seiyaku, Co , Ltd. ("Teikoku"). Teikoku is the only manufacturer approved by the Food and Drug Administration (FDA) anywhere in the world to manufacture and supply Lidoderm® for the U S. market. Endo is the exclusive distributor of Lidoderm® in the U S Teikoku and the U S developer, Hind

Healthcare, Inc., are the owners of the approved NDA (new drug application) and the patent for the development of the product

B. Marketing History

On October 24, 1995, FDA designated Lidoderm® as an "orphan drug" for the relief of allodynia (painful hypersensitivity) and chronic pain in post-herpetic neuralgia (see Attachment 3). An orphan drug is a drug intended to treat a rare condition that affects fewer than 200,000 persons in the U S , or affects more than 200,000 persons but for which there is no reasonable expectation that the cost of developing and making available the drug will be recovered from sales.[1] The orphan drug provisions of the Federal Food, Drug, and Cosmetic Act (FDC Act) are intended to encourage the development and marketing of drugs for rare diseases, through the use of certain economic incentives [2] Without these economic incentives, the rare condition would go untreated with drugs Attachment 4 explains in more detail the nature of orphan drugs.

FDA approved Lidoderm® for marketing for the relief of pain associated with post-herpetic neuralgia on March 19, 1999 (see Attachment 5). The FDA-approved package insert for Lidoderm® is Attachment 6 Endo began marketing Lidoderm® on September 15, 1999, and 123,572 cartons have been distributed since then

The dispensing statistics available to Endo at this time show that the average prescription size for Lidoderm® since launch of the product is 28 7 patches, which equals almost six (5 74) envelopes (one carton). For the first quarter of this year, the average prescription size increased to 29 1 patches, which also equals about six (5 82) envelopes.

C Patient Need for Lidoderm®

Lidoderm® is the only drug that FDA has approved for the relief of pain associated with postherpetic neuralgia. Postherpetic neuralgia is a neuropathic pain syndrome that is

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1 21 U S C § 360bb(a)(2)

2 See, e g., 21 U S C § 360cc

most commonly defined as pain persisting or recurring in the region of herpes zoster (shingles) eruption at least one month after the rash has healed.[3]

Postherpetic neuralgia is characterized by three types of pain: (1) a constant, deep, aching or burning pain, (2) an intermittent pain with a sharp, lancinating or jabbing quality; and (3) a dysesthetic pain provoked by normally innocuous stimuli, such as light touch, heat, or cold (allodynia), that lasts well beyond the duration of the stimulus (hyperpathia) Paradoxically, in addition to this painful hypersensitivity, patients with postherpetic neuralgia may develop concomitant sensory deficit, experiencing, for example, a sensation of numbness within the painful area. These sensory abnormalities may extend well beyond the boundary of the initial herpes zoster eruption.[4]

The risk of developing postherpetic neuralgia increases with age, and the elderly are at a greatly increased risk. Approximately 27% of patients over age 55, 47% of patients over age 60, and 73% of patients over age 70 develop postherpetic neuralgia after having shingles [5] Thus, the vast majority of patients who use Lidoderm® are the elderly

Because the pain of postherpetic neuralgia may become intractable over a period of months to years, postherpetic neuralgia can prevent patients from carrying on normal daily activities such as dressing, bathing, grooming (due to tactile allodynia), traveling, shopping, and cooking Tactile allodynia may result in such unbearable pain that patients are unable to wear clothing on the affected body part, potentially restricting their ability to venture outside the home and contributing to their social isolation The cumulative effect of these factors is a significant reduction in the patients' quality of life and increased use of healthcare resources.[6]

Because of the complex etiology of postherpetic neuralgia, its treatment has typically involved the empirical use of traditional analgesic and anesthetic drugs, opioids,

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[3] Irving GA, Wallace MS, Herpes zoster and postherpetic neuralgia In *Pain Management for the Practicing Physician* Philadelphia, PA Churchill Livingstone, 1997 141-147

[4] Choo PW, Galil K, Donahue JG, Walker AM, Spiegelman D, Platt R Risk factors for postherpetic neuralgia *Arch Intern Med.* 1997, 157 1217-1224

[5] Kost RG, Straus SE Postherpetic neuralgia-pathogenesis, treatment, and prevention *N Engl J Med.* 1996,335 32-42

[6] Schmader K Postherpetic neuralgia in immunocompetent elderly people *Vaccine* 1998, 16 1768-1770

capsaicin, and neuroactive agents such as tricyclic antidepressants and antiepileptic drugs. Variable success has also been reported with transcutaneous electrical nerve stimulation (TENS), nerve blocks and, as a last resort, surgery.[7] However, none of these medications or therapeutic modalities have been approved by FDA for the treatment of postherpetic neuralgia.

Lidoderm® is the first and only treatment approved by FDA specifically for the relief of pain associated with postherpetic neuralgia With its unique delivery system, and when applied directly to intact skin, Lidoderm® penetrates the skin, soft tissues, and peripheral nerves without producing clinically significant serum drug levels and with little risk of systemic side effects or complete anesthetic block

With few side effects, Lidoderm® can fill some of the tremendous need for pain relief that exists in this patient population. As confirmation of this unmet medical need, Attachment 7 consists of several histories of sufferers of postherpetic neuralgia who participated in the clinical trials for Lidoderm® and whose pain was significantly relieved by Lidoderm®, as well as some testimonials of new patients since launch.

D How Lidoderm® is Used

Upon reactivation, the virus that causes shingles will spread along a nerve to the skin, erupting in multiple places along the skin following the entire nerve This broad distribution of pain may require up to three patches to cover as much of the painful areas as possible

The recommended dosage is up to three patches, once for up to 12 hours, within a 24-hour period. Typical parts of the body where Lidoderm® is applied are as follows torso, >50%, face/eye area, 20%, lower back and neck, 20% In addition, as seen in the following figure, significant portions of patients have pain for longer than one year [8]

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[7] Gershon AA Epidemiology and management of postherpetic neuralgia *Semin Dermatol* 1996,15 (suppl 1) 8-13

[8] De Moragas JM, Kierland RR, The outcome of patients with herpes zoster Archives of Dermatology 1957, 75.193-6

Figure 2 Patients with Post Herpetic Neuralgia lasting over 1 year

II REGULATION AT ISSUE

On April 10, 1995, four years before Lidoderm® was approved for marketing, the Commission published a final rule (effective April 10, 1996) providing that "products containing more than 5 0 mg of lidocaine in a single package (i e , retail unit) shall be packaged" in child-resistant packaging.[9]

In December of 1998, Endo asked this law firm to investigate the applicability of the standard to lidocaine patches. A review of the notice of proposed rulemaking,[10] the 1992 Briefing Package of the Commission's Directorate for Health Sciences, and the final rule, revealed that the Commission made the findings required by the Poison Prevention

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9 60 Fed Reg 17992, codified at 16 C F R. § 1700 14(a)(23)

10 57 Fed Reg 34274 (Aug 4, 1992)

Packaging Act (PPPA) only with respect to (1) the following dosage forms: "creams, ointments, gels, jellies, viscous solutions, liquids, sprays, aerosols, and injectables," and (2) the following types of packaging: "tube packaging," "squeeze or pump bottles," and "aerosol sprays "[11] The Commission considered also prefilled syringes and a product "in a foil packet containing 1/8 oz of gel."[12]

Because the findings required by the PPPA were not made with respect to lidocaine patches, and based on well-settled principles of administrative law, we concluded that the regulation could not be construed to apply to lidocaine patches, either reasonably or legally In addition, on December 10, 1998, a representative of this law firm discussed the applicability of the regulation with a member of the Commission's staff, who was identified as the contact person for the child-resistant packaging regulations We were informed that the standard for lidocaine products was not intended to apply to lidocaine patches because they were not on the market at the time the standard was proposed and finalized. The staffer added that the Commission was "in the process of formulating its policy on patch products "[13]

Thus, even after consulting with Commission staff, Endo had no reason to believe that the standard would apply to lidocaine patches However, in a June 14, 1999 letter to Endo, the Commission staff stated that Lidoderm® was required to comply with the standard

III. INAPPLICABILITY OF REGULATION TO LIDOCAINE PATCHES

In previous correspondence, Endo has explained the bases for its position that the standard legally cannot be interpreted to apply to lidocaine patches, that the Commission does not have statutory authority to enforce the standard against lidocaine patches, and that Endo's Lidoderm® therefore is not misbranded under section 502(p) of the FDC Act. Endo's arguments in this regard are set forth in its letters of June 29, 1999 and September 7, 1999, which are included as Attachments 8 and 9 to this petition, and incorporated by reference

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[11] See, e g., 60 Fed Reg at 17993-94, 18002-03

[12] Id at 17994, 18001

[13] The Commission staff have indicated that we misunderstood the statements that were made

IV ENDO'S VOLUNTARY COMPLIANCE

Despite the inapplicability of the regulation to Lidoderm®, Endo has been working with the staff at trying to find a mutually satisfactory resolution As the first step, and without admitting the applicability of the regulation to Lidoderm®, Endo petitioned for a stay of enforcement, which stay was granted by letter of June 2, 2000

As an interim (short-term) voluntary compliance measure, Endo has obtained child-resistant recloseable pouches. A sample of this pouch is enclosed as Attachment 10 Effective August 1, 2000, each carton of Lidoderm® shipped to customers contains one of these child-resistant pouches. Endo has sent a letter to pharmacists (Attachment 11) informing them of the availability of the pouches, and instructing them to dispense Lidoderm® only in the child-resistant pouches Each child-resistant pouch can hold six Lidoderm® envelopes, which is the current average prescription size. In addition, a statement was added to the Lidoderm® carton and the child-resistant pouch to emphasize that the product must be dispensed in the child-resistant pouch (see Attachments 10 and 12)

In exploring a permanent voluntary compliance measure, Endo considered packaging the five patches in a resealable, child-resistant envelope However, no such packaging is currently available As explained in section V of this petition, it is not practicable to package each Lidoderm® patch in a child-resistant envelope Thus, as the permanent voluntary compliance measure, Endo has determined that the only viable alternative is to replace the current carton with the child-resistant pouch that is now being included inside the carton. The child-resistant pouch would be labeled with the same information that now appears on the carton.

A detailed timeline has been developed for implementing this permanent solution (see Attachment 13). This permanent solution can be implemented, and product in a child-resistant pouch can be available to customers, by May 31, 2001 This would eliminate the need for the pharmacist to place the product in a child-resistant container, as all Lidoderm® would be supplied in a child-resistant pouch containing 30 patches (six envelopes). The labeling would also be revised to instruct patients to always store the envelopes inside the child-resistant pouch.

For this permanent solution, Teikoku, the manufacturer, will need to purchase a heat-sealing machine at a cost of [redacted] The heat-sealing machine is

necessary to seal the child-resistant pouch once the envelopes are placed inside it The child-resistant pouch will be supplied to Teikoku with the zipper in the closed and locked position, with the top of the pouch left open. Teikoku will place six envelopes into the child-resistant pouch through the open top and then pass the top of the child-resistant pouch through the heat-sealing machine to seal it closed

The cost to manufacture and package six envelopes (each containing five patches) into the child-resistant pouch is estimated to be [redacted] increase over the current cost of goods, due to the additional labor and material cost. Additional labor is necessary because the current method for packaging the envelopes into a carton is not the same method used to place the envelopes into the child-resistant pouch method

Currently, as the envelopes come off the packaging/sealing line, they move on a conveyor belt where they are manually placed directly into the carton, the carton is sealed, and placed into shippers (cardboard box containing sixteen cartons) To package the envelopes into the child-resistant pouch, the envelopes must be first transported to a different room which houses the heat sealing machine, because there is no space for the heat sealing machine in the room currently used to package the envelopes into cartons The child-resistant pouches then must be manually and individually opened, and "formed" so that the six envelopes will fit inside Once the six envelopes are placed inside, the top of the child-resistant pouch must be heat-sealed, and placed into a shipper. Teikoku estimates that this procedure is more labor intensive, will take longer, and therefore will be more expensive to complete In addition, the cost of the child-resistant pouch is estimated to be [redacted] whereas that of the carton is on[redacted]

Additional burdens to making these changes to the packaging process would be the required notifications to FDA relating to the changes in the secondary packaging and the use of an additional room for heat-sealing the pouches

Nevertheless, Endo and Teikoku are willing to undertake this massive endeavor to cooperate with the Commission because the alternative proposed by the Commission staff will destroy the marketability of the product.

V NEED FOR RELIEF

The Commission staff have informed Endo that <u>each</u> patch of Lidoderm® must be in a child-resistant envelope. This is apparently based on the definition of "package" in the

PPPA, which refers to the "immediate" container [14] Endo has determined that the costs involved in this approach will be prohibitive

Teikoku has assessed the feasibility of packaging each Lidoderm® patch in a child-resistant envelope and informed Endo that its current equipment cannot accommodate the thicker child-resistant material that is used for packaging the EMLA® patch. [15] The EMLA® material is thicker and less pliable than the material used to make the Lidoderm® envelope Teikoku has four machines that have been validated to package Lidoderm® in the current envelopes If Teikoku were to package each Lidoderm® patch in a child-resistant envelope, Teikoku would need to purchase four new envelope-processing machines capable of handling the child-resistant material. Teikoku estimates that the capital cost alone for these new machines would be [redacted] per machine)

Teikoku would also incur the costs for re-engineering the plant to accommodate the new equipment, performing installation qualification, performance qualification, and operational qualification, repeating stability studies in the new material, and submitting these data for prior approval to the FDA. These additional costs are estimated at half a million dollars. The total estimated cost would be [redacted] broken down as follows

Activity	Cost
Purchase three new machines	[redacted]
Manufacture three FDA submission batches	[redacted]
Extended specification compliance testing on all three batches	[redacted]
Accelerated stability testing	[redacted]
Real-time stability testing	[redacted]
+/- 10%	
Total	[redacted]

Manufacturing and packaging one patch per envelope would result in an increase of [redacted] in the cost of manufacturing Lidoderm® because there would be significant increases

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[14] 15 U S C § 1471(3)

[15] The Commission staff have informed Endo that the EMLA® patch is contained in a child-resistant foil packet

in the amount of labor and materials (five envelopes with one patch each versus the current one envelope with five patches). Teikoku estimated that the labor would increase from four days to 20 days of production to manufacture and package an equivalent amount of patches. If this approach for packaging Lidoderm® were to be taken, Endo would incur a negative [redacted] profit margin at the current price of Lidoderm®.

Currently, Teikoku has the capacity to manufacture 700,000 patches and package 140,000 envelopes in one day. The process for manufacturing 700,000 patches includes manufacturing 14 batches (700 kg) of "lidocaine paste" and applying it to the patch material in a single day. The process includes an overnight curing time before the patches are put into the envelopes. The patches must be packaged in the envelopes within 24 hours of being manufactured. After the Lidoderm® patches have cured overnight in stacks of five, each stack of five patches is placed into an envelope and sealed.

If Teikoku were to manufacture and package one patch per envelope, only 140,000 patches could be made in one day because of the limitation in the capacity to package 140,000 envelopes per day. Thus, it would take *five times* as long to produce an equivalent amount of product under the one-patch to one-envelope scenario (700,000/140,000).

Teikoku allocates four days a month for the production of Lidoderm®. Thus, if each patch must be packaged in its own envelope, an additional 16 days would be needed to produce the same amount of Lidoderm® currently produced. These additional 16 days are not available because other Teikoku customers use the remainder of their production time each month. It would be an undue burden for Teikoku to accommodate this kind of change in their production schedule or take time from other customers' production needs. In addition, Teikoku, the only FDA-approved manufacturing site for Lidoderm®,[16] is not willing to transfer this manufacturing technology to another manufacturer since the manufacturing process is proprietary technology belonging solely to Teikoku.

The above discussion does not even take into consideration that existing child-resistant envelopes might not prove suitable for Lidoderm®, as no testing has been done to make this determination. Due to the uniqueness of the Lidoderm® technology, what might be suitable for other lidocaine patches, or for other patch products in general, might

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[16] Under the FDC Act, a new drug may be manufactured only in a facility and using a process that FDA has approved as part of the new drug application for the product.

nevertheless fail to adequately protect the integrity of Lidoderm® or might interfere with its intended storage or use [17]

In summary, the current technology and set-up at Teikoku's manufacturing plant does not lend itself to the immediate package being child-resistant for both economical and practical reasons. If Endo were forced to package each patch in a child-resistant envelope, Endo could not continue marketing Lidoderm®, and this orphan drug would no longer be available to patients in the United States.

Therefore, the only permanent solution that would allow Endo to continue marketing the product is to manufacture and sell Lidoderm® in a child-resistant pouch containing six envelopes, each envelope containing five patches

VI. NO CHILDREN POISONINGS WITH LIDODERM®

Neither Endo nor Teikoku has ever received a report of a child being prescribed Lidoderm® No adverse events or accidental exposures attributed to children have ever been reported. The world literature is bereft of any reports of Lidoderm® poisoning The American Association of Poison Control Centers informed Endo that, as of August 9, 2000, there were no reports of overdosing, accidental exposure, or poisoning by children with Lidoderm®

As stated above, application of three Lidoderm® patches to the skin for 12 hours results in a peak plasma level of 0 13 µg/mL This is about 20 times less than the amount at which lidocaine begins to have any systemic effects (2-5 µg/mL) [18] It should be noted that the lowest blood level of lidocaine mentioned in the Commission's 1992 Briefing Package as having an adverse effect on a child was 4 5 µg/ml, measured six hours after oral

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[17] One of the findings that the PPPA requires the Commission to make in order to impose a special packaging requirement is that the special packaging be "appropriate " 60 Fed Reg at 8002 "Appropriateness" exists when packaging complying with the standard will adequately protect the integrity of the substance and not interfere with the intended storage or use *Id*

[18] 1992 Briefing Package for lidocaine products, at 56

administration of a liquid preparation to a five-month old child [19] Thus, skin contact with Lidoderm® should not present a risk of serious injury or illness to a child [20]

In addition, unlike other dosage forms of lidocaine (creams, ointments, jellies, liquids, sprays, which were the dosage forms evaluated by the Commission in the rulemaking for lidocaine products), access to lidocaine from Lidoderm® is not easily had A child would need to chew or suck on a portion of the patch (which is too big to be placed entirely in the mouth) for a certain amount of time before any lidocaine would begin to be absorbed through the mucosa of the mouth or swallowed. As explained above, there is no readily-available "reservoir" of lidocaine in Lidoderm®—the lidocaine is embedded in and part of the adhesive to control its release from the patch Thus, Lidoderm® does not present the same degree of poisoning risk to children as other lidocaine products

VII. THE COMMISSION HAS AUTHORITY TO GRANT THIS PARTIAL EXEMPTION

Both the Commission's regulations[21] and the legislative history of the PPPA[22] provide that the Commission has broad discretion to "exempt categories of substances subject to special packaging requirements" and "provide such exemptions while prescribing such special packaging requirements" or by subsequently amending the prescribing regulation. The Commission also has power "to determine specifically the parameters of special packaging "[23]

VIII CONCLUSION

The PPPA instructs the Commission to take into consideration the technical feasibility, practicability, and appropriateness of a special packaging standard [24] Endo's situation as explained in this petition perfectly illustrates the importance of these considerations Congress did not intend to authorize the Commission to destroy the

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19 *Id*, at 57 (the child recovered fully within 24 hours)

20 For purposes of this discussion, Endo is assuming that the PPPA was intended to prevent this type of poisoning (non-ingestion), although this is not clear

21 16 C F R § 1702 1

22 H Rep No 91-1755 at 9 (1970)

23 S Rep No 91-845 at 9 (1970)

24 15 U S C § 1472(a)(1)

viability of a product or to take a position that has the practical result of "banning" a product, particularly one intended to ease human suffering

Based on the above, Endo Pharmaceutical respectfully petitions the Commission to authorize Endo to comply with the special packaging standard at 16 C F.R. § 1700 14(a)(23) by using a child-resistant outer container.

Respectfully submitted,

HYMAN, PHELPS & MCNAMARA, P.C
Counsel for Endo Pharmaceuticals, Inc.

By Samia N Rodriguez

SNR/dng

ATTACHMENTS

TABLE OF CONTENTS

TAB ONE IS CONFIDENTIAL

FRONT OF BOX

ENDO LABORATORIES

Endo® LIDODERM®

(lidocaine patch 5%)

LOT:

EXP:

N 3 63481-687-06 2

NDC 63481-687-06

ENDO LABORATORIES

Endo® LIDODERM®

(lidocaine patch 5%)

Each adhesive patch contains:
Lidocaine..... 700 mg (50 mg per gram adhesive) in an aqueous base. Methylparaben and propylparaben as preservatives.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Package not child resistant. Keep used and unused patches out of the reach of children and pets.

R_x only

30 PATCHES (6 envelopes containing 5 patches each)

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
TEIKOKU SEIYAKU CO.,LTD.
Sanbonmatsu, Kagawa 769-2695
Japan

BACK OF BOX

ENDO LABORATORIES
Endo® LIDODERM®
(lidocaine patch 5%)

NDC 63481-687-06

ENDO LABORATORIES

Endo® LIDODERM®

(lidocaine patch 5%)

Each adhesive patch contains:
Lidocaine..... 700 mg (50 mg per gram adhesive) in an aqueous base. Methylparaben and propylparaben as preservatives.

DOSAGE: For dosage and full prescribing information, read accompanying product information.

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

WARNING: Package not child resistant. Keep used and unused patches out of the reach of children and pets.

R_x only

30 PATCHES (6 envelopes containing 5 patches each)

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
TEIKOKU SEIYAKU CO.,LTD.
Sanbonmatsu, Kagawa 769-2695
Japan

87770B

FRONT OF ENVELOPE

Cut along dotted line and pull open seal

IMPORTANT
Reseal after opening

NDC 63481-687-05

ENDO LABORATORIES

Endo® LIDODERM®

(lidocaine patch 5%)

Each adhesive patch contains:
Lidocaine .....700 mg (50 mg per gram adhesive) in an aqueous base. Methylparaben and propylparaben as preservatives.

***DOSAGE*: For dosage and full prescribing information, read accompanying product information.**

Store at 25°C (77°F); excursions permitted to 15°-30°C (59°-86°F).

***WARNING*: Package not child resistant. Keep used and unused patches out of the reach of children and pets.**

R_x only

5 PATCHES (10 CM X 14 CM EACH)

Manufactured for:
Endo Pharmaceuticals Inc.
Chadds Ford, PA 19317

Manufactured by:
TEIKOKU SEIYAKU CO.,LTD.
Sanbonmatsu, Kagawa 769-2695
Japan

BACK OF ENVELOPE

DIRECTIONS FOR USE

Cut the outer seal from the package along the dotted line and pull apart the zipper seal.

Remove the desired number of patches and reseal the package using pressure on the zipper seal. The adhesive contains water and will dry out if the package is open.

Remove the transparent release liner before application of patches to the skin.

Apply up to three (3) LIDODERM® patches at one time to cover the most painful area. Apply patches only once for up to 12 hours in a 24-hour period. Remove patches if irritation occurs.

N 3 63481-687-05 5

9437/OB

LOT: 6916

EXP: 2002.05

LIST OF ORPHAN PRODUCTS DESIGNATIONS AND APPROVALS

Through December 31, 1998

NAME Generic Name TN=Trade Name	INDICATION DESIGNATED	SPONSOR & ADDRESS DD=Date Designated MA=Marketing Approval
Levocarnitine TN= Carnitor	Treatment of zidovudine-induced mitochondrial myopathy	Sigma-Tau Pharmaceuticals, Inc. 800 S. Frederick Avenue, Suite 300 Gaithersburg, MD 20877 DD=04/07/1997 MA= / /
Levomethadyl acetate hydrochloride TN= Orlaam	Treatment of heroin addicts suitable for maintenance on opiate agonists	Biodevelopment Corporation 8180 Greensboro Drive, Suite 1000 McLean, VA 22102 DD=01/24/1984 MA=07/09/1993
Lidocaine patch 5% TN= Lidoderm Patch	For relief of allodynia (painful hypersensitivity), and chronic pain in post-herpetic neuralgia.	Hind Health Care, Inc. 3707 Williams Rd., Suite 101 San Jose, CA 95117 DD=10/24/1995 MA= / /
Liothyronine sodium injection TN= Triostat	Treatment of myxedema coma/precoma.	SmithKline Beecham Pharmaceuticals One Franklin Plaza P O Box 7929 Philadelphia, PA 19101 DD=07/30/1990 MA=12/31/1991
Lipid/DNA human cystic fibrosis gene TN=	Treatment of cystic fibrosis	Genzyme Corporation P O Box 9322 One Mountain Road Framingham, MA 01701 DD=04/08/1996 MA= / /
Liposomal Cyclosporin A TN= Cyclospire	For aerosolized administration in the prevention and treatment of lung allograft rejection and pulmonary rejection events associated with bone marrow transplantation.	Vernon Knight, M D. Baylor College of Medicine, Dept. of Molecular Physiology One Baylor Plaza Houston, TX 77030 DD=04/30/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of osteosarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of Ewing's sarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal amphotericin B TN= AmBisome	Treatment of cryptococcal meningitis.	Fujisawa USA, Inc. 3 Parkway North Center Deerfield, IL 60015 DD=12/10/1996 MA=08/11/1997

APPROVED DRUG PRODUCTS WITH THERAPEUTIC EQUIVALENCE EVALUATIONS

U.S. Food and Drug Administration

OOPD Program Overview

Purpose of the Orphan Products Program

The Office of Orphan Products Development (OOPD) located in the Office of the Commissioner, Food and Drug Administration (FDA), administers the orphan products development program This program is essentially involved in the identification of orphan products and the facilitation of their development Although the OOPD Grants Program has been expanded to include clinical studies for medical foods and devices that meet the "orphan" criteria established by Congress, the Orphan Drug Act pertains primarily to drug and biological products

This introduction will provide a general overview of the organization and operation of the orphan products program at FDA. For further guidance and direction, additional and more specific information is available on the topics covered here

Congressional Action

The Orphan Drug Act (P L 97-414) amended the Federal Food, Drug and Cosmetic Act (FFDCA) as of January 4, 1983 Additional orphan drug amendments were passed by Congress in 1984, 1985 and 1988 The use of the term "orphan", as in "orphan drug", "orphan" disease, etc , does not actually appear in the text of the law which focuses upon definitions of and treatments for "rare diseases and conditions"

The 1983 Orphan Drug Act guarantees the developer of an orphan product seven years of market exclusivity following the approval of the product by the FDA As a result of the Orphan Drug Act, the following procedures are administered by the Office of Orphan Products Development

- Reviewing and approving requests for orphan product designation
- Overseeing the orphan product program that gives sponsors seven years of exclusive marketing for orphan products
- Coordinating research study design assistance for sponsors of drugs for rare diseases
- Encouraging sponsors to conduct open protocols, allowing patients to be added to ongoing studies
- Awarding grant funding to defray costs of qualified clinical testing incurred in connection with the development of drugs for rare diseases and conditions

The original definition of "rare disease or condition" in the Orphan Drug Act was amended in October 1984 by P L 98-551 to add a numeric prevalence threshold to the definition

> " the term rare disease or condition means any disease or condition which (a) affects less than 200,000 persons in the U S or (b) affects more than 200,000 persons in the U S but for which there is no reasonable expectation that the cost of developing and making available in the U S a drug for such disease or condition will be recovered from sales in the U S of such drug "

Prior to this revision of the Orphan Drug Act; every sponsor was required to provide financial

information regardless of the size of the proposed target patient population A product may still be designated as an orphan by demonstrating that the financial criteria of the law are applicable, regardless of the number of patients affected

P L 100-290 amended the Orphan Drug Act on April 18, 1988, and requires that the application for designation be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA) Prior to this amendment, the designation request could be filed at any time prior to FDA's approval to market the product

Section 1205 of P L 104-188 reinstated the tax credits for clinical testing expenses of orphan drugs for the period July 1, 1996 to May 31, 1997 and allows these credits to be carried forward/back like some other business tax credits.

The Orphan Drug Final Regulations were published in the Federal Register on December 29, 1992, and became effective thirty days thereafter

Orphan Drug Designation

In order for a sponsor to obtain orphan designation for a drug or biological product, an application must be submitted to OOPD, and the designation approved The approval of an application for orphan designation is based upon the information submitted by the sponsor A drug that has obtained orphan designation is said to have "orphan status " Each designation request must stand on its own merit Sponsors requesting designation of the same drug for the same indication as a previously designated product must submit their own data in support of their designation request The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval Safety and efficacy of a compound must be established through adequate and well-controlled studies

Incentives of the Orphan Drug Act

The Orphan Drug Act (P L 97-414, as amended) includes various incentives that have stimulated a considerable amount of interest in the development of orphan drug and biological products These incentives include tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, and seven years of marketing exclusivity for a designated drug or biological product approved by the FDA

Section 527 of the Orphan Drug Act provides a seven-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan drug or biological product Exclusivity begins on the date that the marketing application is approved by FDA for the designated orphan drug, and applies only to the indication for which the drug has been designated and approved A second application for the same drug for a different use could be approved by FDA.

Final regulations on the tax credits were published in the Federal Register on October 3, 1988 (53 FR 38708), and the current version of these regulations are in Title 26, Code of Federal Regulations, Section 45c The Internal Revenue Service administers the tax credit provisions, and specific questions about the interpretation of the law or regulations affecting the applicability of the tax credit provision of the Act should be directed to IRS If more information on tax credits is needed, contact Pass Through and Special Industries Division, Office of the Chief Counsel, Internal Revenue Service, 1111 Constitution . Avenue, NW, Washington, DC 20224, telephone is (202) 622-3120

Protocol Assistance

Section 525 of the Orphan Drug Act provides for formal protocol assistance when requested by the sponsors of drugs for rare diseases or conditions The formal review of a request for protocol assistance is the direct responsibility of the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER), depending on which Center has authority for review of the product. The Office of Orphan Products Development (OOPD) is responsible for insuring that the request qualifies for consideration under section 525 of the FFDCA. This includes determining "whether there is reason to believe the sponsor's drug is a drug for a disease or condition that is rare in the United States " A sponsor need not have obtained orphan drug designation to receive protocol assistance

Once OOPD determines that the proposed compound is for a disease or condition that is rare in the U S , the request will be forwarded to the responsible reviewing division for formal review and direct response OOPD monitors the review process within the respective CDER/CBER reviewing division and, where possible, assists in resolving specific issues that may arise during the review process It should be understood that protocol assistance provided under the Act does not waive the necessity for the submission of an Investigational New Drug Application (IND) by sponsors planning to conduct clinical trials with the product

Research Grants

The FDA, through OOPD, funds the development of orphan products through its grants program for clinical studies The Request for Applications (RFA) announcing availability of funds is published in the Federal Register each year - usually in June Eligibility for grant funding is extended to medical devices and medical foods for which there is no reasonable expectation of development without such assistance Applications are reviewed by panels of outside experts and are funded by priority score

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville MD 20857

NDA 20-612

MAR 19 1999

Hind Health Care, Inc.
Attention: Larry Caldwell, Ph.D.
Consultant to Hind Health Care, Inc.
3707 Williams Road Suite 101
San Jose, CA 95117-2017

Dear Dr. Caldwell:

Please refer to your new drug application (NDA) dated May 31, 1996, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Lidoderm Patch (lidocaine patch) 5% w/w. Please refer to our not approvable letter dated April 17, 1997, and our approvable letter dated December 2, 1998.

We acknowledge receipt of your submission dated January 15, 1999. This submission, together with your submissions of August 30, October 30, and December 1, 1997; February 9, 1999, and March 4, 1999, and correspondence via facsimile transmission dated March 15 and 18(two), 1999, constituted a complete response to our December 2, 1998, action letter.

This new drug application provides for the use of Lidoderm Patch (lidocaine patch) 5% w/w for the treatment of pain in post-herpatic neuralgia.

We have completed the review of this application, as amended, and have concluded that adequate information has been presented to demonstrate that the drug product is safe and effective for use as recommended in the agreed upon labeling text. Accordingly, the application is approved effective on the date of this letter

The final printed labeling (FPL) must be identical to the submitted draft labeling (package insert submitted March 4 and 18, 1999, immediate container and carton labels submitted March 15, 1999). Marketing the product with FPL that is not identical to the approved labeling text may render the product misbranded and an unapproved new drug.

Please submit 20 copies of the FPL as soon as it is available, in no case more than 30 days after it is printed. Please individually mount ten of the copies on heavy-weight paper or similar material. For administrative purposes, this submission should be designated "FPL for approved NDA 20-612." Approval of this submission by FDA is not required before the labeling is used.

Validation of the regulatory methods has not been completed. At the present time, it is the policy of the Center not to withhold approval because the methods are being validated. Nevertheless, we expect your continued cooperation to resolve any problems that may be identified.

In addition, please submit three copies of the introductory promotional materials that you propose to use for this product. All proposed materials should be submitted in draft or mock-up form, not final print. Please submit one copy to this Division and two copies of both the promotional materials and the package insert directly to:

Division of Drug Marketing, Advertising, and Communications, HFD-40
Food and Drug Administration
5600 Fishers Lane
Rockville, Maryland 20857

Please submit one market package of the drug product when it is available.

We remind you that you must comply with the requirements for an approved NDA set forth under 21 CFR 314.80 and 314.81.

If you have any questions, contact Victoria Lutwak, Project Manager, at (301) 827-2090.

Sincerely,

/S/

John E. Hyde Ph.D., M.D.
Deputy Director
Division of Anti-Inflammatory, Analgesic and
Ophthalmic Drug Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research

cc:
Archival NDA 20-612
HFD-550/Div. Files
HFD-550/V.Lutwak
HFD-550/ J Hyde/ C Fang/ H Patel/ C Yaciw
HF-2/MedWatch (with labeling)
HFD-002/ORM (with labeling)
HFD-105/ADRA (with labeling)
HFD-40/DDMAC (with labeling)
HFD-613/OGD (with labeling)
HFD-21/ACS (with labeling) - for drug discussed at advisory committee meeting.
HFD-35/Orphan Drugs
HFD-95/DDMS (with labeling)
HFD-830/DNDC Division Director
DISTRICT OFFICE

Drafted by: vl/March 10, 1999
Initialed by: vl
final:
filename: v/NDA/20612/990319AP

APPROVAL (AP)

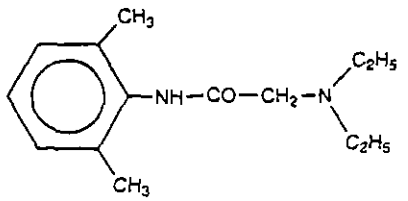
Endo®
ENDO LABORATORIES

6524 00

LIDODERM®
(lidocaine patch 5%)

DESCRIPTION
LIDODERM (lidocaine patch 5%) is comprised of an adhesive material containing 5% lidocaine which is applied to a non-woven polyester felt backing and covered with a polyethylene terephthalate (PET) film release liner The release liner is removed prior to application to the skin The size of the patch is 10 cm x 14 cm

Lidocaine is chemically designated as acetamide 2-(diethylamino)-N-(2 6-dimethylphenyl) has an octanol water partition ratio of 43 at pH 7 4 and has the following structure



Each adhesive patch contains 700 mg of lidocaine (50 mg per gram adhesive) in an aqueous base It also contains the following inactive ingredients dihydroxyaluminum aminoacetate disodium edetate, gelatin glycerin, kaolin methylparaben polyacrylic acid polyvinyl alcohol, propylene glycol, propylparaben sodium carboxymethylcellulose sodium polyacrylate D-sorbitol tartaric acid and urea

CLINICAL PHARMACOLOGY
Pharmacodynamics
Lidocaine is an amide-type local anesthetic agent and is suggested to stabilize neuronal membranes by inhibiting the ionic fluxes required for the initiation and conduction of impulses

The penetration of lidocaine into intact skin after application of LIDODERM is sufficient to produce an analgesic effect but less than the amount necessary to produce a complete sensory block

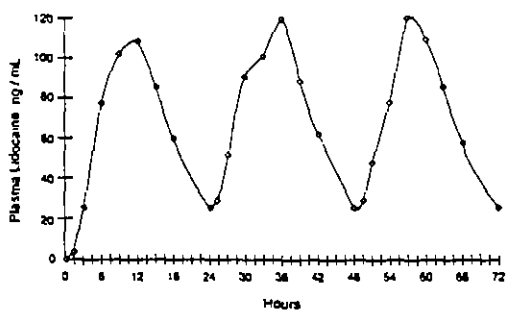
Pharmacokinetics
Absorption
The amount of lidocaine systemically absorbed from LIDODERM is directly related to both the duration of application and the surface area over which it is applied In a pharmacokinetic study three LIDODERM patches were applied over an area of 420 cm^2 of intact skin on the back of normal volunteers for 12 hours Blood samples were withdrawn for determination of lidocaine concentration during the application and for 12 hours after removal of patches The results are summarized in Table 1

Table 1
Absorption of lidocaine from LIDODERM
Normal volunteers (n = 15 12-hour wearing time)

LIDODERM Patch	Application Site	Area (cm^2)	Dose Absorbed (mg)	C_{max} (µg/mL)	T_{max} (hr)
3 patches (2100 mg)	Back	420	64 ± 32	0 13 ± 0 06	11 hr

When LIDODERM is used according to the recommended dosing instructions only 3 ± 2% of the dose applied is expected to be absorbed At least 95% (665 mg) of lidocaine will remain in a used patch Mean peak blood concentration of lidocaine is about 0 13 µg/mL (about 1/10 of the therapeutic concentration required to treat cardiac arrhythmias) Repeated application of three patches simultaneously for 12 hours (recommended maximum daily dose) once per day for three days indicated that the lidocaine concentration does not increase with daily use The mean plasma pharmacokinetic profile for the 15 healthy volunteers is shown in Figure 1

Figure 1
Mean lidocaine blood concentrations after three consecutive daily applications of three LIDODERM patches simultaneously for 12 hours per day in healthy volunteers (n = 15)



Distribution
When lidocaine is administered intravenously to healthy volunteers the volume of distribution is 0 7 to 2 7 L/kg (mean 1 5 ± 0 6 SD n = 15) At concentrations produced by application of LIDODERM lidocaine is approximately 70% bound to plasma proteins primarily alpha-1-acid glycoprotein At much higher plasma concentrations (1 to 4 µg/mL of free base), the plasma protein binding of lidocaine is concentration dependent Lidocaine crosses the placental and blood brain barriers presumably by passive diffusion

Metabolism
It is not known if lidocaine is metabolized in the skin Lidocaine is metabolized rapidly by the liver to a number of metabolites including monoethylglycinexylidide (MEGX) and glycinexylidide (GX) both of which have pharmacologic activity similar to but less potent than that of lidocaine A minor metabolite 2 6-xylidine has unknown pharmacologic activity but is carcinogenic in rats The blood concentration of this metabolite is negligible following application of LIDODERM (lidocaine patch 5%) Following intravenous administration MEGX and GX concentrations in serum range from 11 to 36% and from 5 to 11% of lidocaine concentrations, respectively

Excretion
Lidocaine and its metabolites are excreted by the kidneys Less than 10% of lidocaine is excreted unchanged The half-life of lidocaine elimination from the plasma following IV administration is 81 to 149 minutes (mean 107 ± 22 SD n = 15) The systemic clearance is 0 33 to 0 90 L/min (mean 0 64 ± 0 18 SD n = 15)

CLINICAL STUDIES
Single-dose treatment with LIDODERM was compared to treatment with vehicle patch (without lidocaine) and to no treatment (observation only) in a double-blind crossover clinical trial with 35 post-herpetic neuralgia patients Pain intensity and pain relief scores were evaluated periodically for 12 hours LIDODERM performed statistically better than vehicle patch in terms of pain intensity from 4 to 12 hours

Multiple-dose two-week treatment with LIDODERM was compared to vehicle patch (without lidocaine) in a double-blind crossover clinical trial of withdrawal-type design conducted in 32 patients who were considered as responders to the open-label *use of LIDODERM prior to the study The constant type of pain was evaluated but not the pain induced by sensory stimuli (dysesthesia)* Statistically significant differences favoring LIDODERM were observed in terms of time to exit from the trial (14 versus 3 8 days at p-value <0 001) daily average pain relief and patient's preference of treatment About half of the patients also took oral medication commonly used in the treatment of post-herpetic neuralgia The extent of use of concomitant medication was similar in the two treatment groups

INDICATION AND USAGE
LIDODERM is indicated for relief of pain associated with post-herpetic neuralgia It should be applied only to intact skin

CONTRAINDICATIONS
LIDODERM is contraindicated in patients with a known history of sensitivity to local anesthetics of the amide type or to any other component of the product

WARNINGS
Accidental Exposure in Children
Even a *used* LIDODERM patch contains a large amount of lidocaine (at least 665 mg) The potential exists for a small child or a pet to suffer serious adverse effects from chewing or ingesting a new or used LIDODERM patch although the risk with this formulation has not been evaluated It is important for patients to store and dispose of **LIDODERM out of the reach of children and pets**

Excessive Dosing
Excessive dosing by applying LIDODERM to larger areas or for longer than the recommended wearing time could result in increased absorption of lidocaine and high blood concentrations leading to serious adverse effects (see ADVERSE REACTIONS Systemic Reactions) Lidocaine toxicity could be expected at lidocaine blood concentrations above 5 µg/mL The blood concentration of lidocaine is determined by the rate of systemic absorption and elimination Longer duration of application application of more than the recommended number of patches smaller patients or impaired elimination may all contribute to increasing the blood concentration of lidocaine With recommended dosing of LIDODERM the average peak blood concentration is about 0 13 µg/mL but concentrations higher than 0 25 µg/mL have been observed in some individuals

PRECAUTIONS
General.
Hepatic Disease
Patients with severe hepatic disease are at greater risk of developing toxic blood concentrations of lidocaine because of their inability to metabolize lidocaine normally

Allergic Reactions
Patients allergic to para-aminobenzoic acid derivatives (procaine tetracaine benzocaine etc) have not shown cross sensitivity to lidocaine However LIDODERM should be used with caution in patients with a history of drug sensitivities especially if the etiologic agent is uncertain

Non-intact Skin
Application to broken or inflamed skin although not tested may result in higher blood concentrations of lidocaine from increased absorption LIDODERM is only recommended for use on intact skin

Eye Exposure
The contact of LIDODERM with eyes although not studied should be avoided based on the findings of severe eye irritation with the use of similar products in animals If eye contact occurs, immediately wash out the eye with water or saline and protect the eye until sensation returns

Drug Interactions
Antiarrhythmic Drugs.
LIDODERM should be used with caution in patients receiving Class I antiarrhythmic drugs (such as tocainide and mexiletine) since the toxic effects are additive and potentially synergistic

Local Anesthetics
When *LIDODERM* is used concomitantly with other products containing local anesthetic agents the amount absorbed from all formulations must be considered

Carcinogenesis, Mutagenesis, Impairment of Fertility
Carcinogenesis.
A minor metabolite, 2 6-xylidine has been found to be carcinogenic in rats The blood concentration of this metabolite is negligible following application of LIDODERM

Mutagenesis
Lidocaine HCl is not mutagenic in Salmonella/mammalian microsome test nor clastogenic in chromosome aberration assay with human lymphocytes and mouse micronucleus test

Impairment of Fertility
The effect of LIDODERM on fertility has not been studied

Pregnancy

Teratogenic Effects. Pregnancy Category B

LIDODERM (lidocaine patch 5%) has not been studied in pregnancy Reproduction studies with lidocaine have been performed in rats at doses up to 30 mg/kg subcutaneously and have revealed no evidence of harm to the fetus due to lidocaine There are however no adequate and well-controlled studies in pregnant women Because animal reproduction studies are not always predictive of human response LIDODERM should be used during pregnancy only if clearly needed

Labor and Delivery

LIDODERM has not been studied in labor and delivery Lidocaine is not contraindicated in labor and delivery Should LIDODERM *be used concomitantly with other products containing lidocaine, total doses contributed by all formulations must be considered*

Nursing Mothers

LIDODERM has not been studied in nursing mothers Lidocaine is excreted in human milk and the milk plasma ratio of lidocaine is 0 4 Caution should be exercised when LIDODERM is administered to a nursing woman

Pediatric Use

Safety and effectiveness in pediatric patients have not been established

ADVERSE REACTIONS

Localized Reactions

During or immediately after treatment with LIDODERM (lidocaine patch 5%) the skin at the site of treatment may develop erythema or edema or may be the locus of abnormal sensation These reactions are generally mild and transient resolving spontaneously within a few minutes to hours In clinical studies with LIDODERM there were no serious reactions reported One out of 150 subjects in a three-week study was discontinued from treatment because of a skin reaction (erythema and hives)

Allergic Reactions:

Allergic and anaphylactoid reactions associated with lidocaine although rare, can occur They are characterized by urticaria angioedema bronchospasm and shock If they occur, they should be managed by conventional means The detection of sensitivity by skin testing is of doubtful value

Systemic (Dose-Related) Reactions.

Systemic adverse reactions following appropriate use of LIDODERM are unlikely, due to the small dose absorbed (see CLINICAL PHARMACOLOGY, Pharmacokinetics) Systemic adverse effects of lidocaine are similar in nature to those observed with other amide local anesthetic agents including CNS excitation and/or depression (light-headedness nervousness apprehension euphoria, confusion dizziness, drowsiness tinnitus, blurred or double vision vomiting sensations of heat, cold or numbness twitching, tremors, convulsions unconsciousness respiratory depression and arrest) Excitatory CNS reactions may be brief or not occur at all in which case the first manifestation may be drowsiness merging into unconsciousness Cardiovascular manifestations *may include bradycardia hypotension and cardiovascular collapse leading to arrest*

OVERDOSAGE

Lidocaine overdose from cutaneous absorption is rare, but could occur If there is any suspicion of lidocaine overdose (see ADVERSE REACTIONS Systemic Reactions) drug blood concentration should be checked The management of overdose includes close monitoring, supportive care and symptomatic treatment Dialysis is of negligible value in the treatment of acute overdose with lidocaine

In the absence of massive topical overdose or oral ingestion evaluation of symptoms of toxicity should include consideration of other etiologies for the clinical effects or overdosage from other sources of lidocaine or other local anesthetics

The oral LD_{50} of lidocaine *HCl* is 459 (346-773) mg/kg (as the salt) in non-fasted female rats and 214 (159-324) mg/kg (as the salt) in fasted female rats which are equivalent to roughly 4000 mg and 2000 mg respectively in a 60 to 70 kg man based on the equivalent surface area dosage conversion factors between species

DOSAGE AND ADMINISTRATION

Apply LIDODERM to intact skin to cover the most painful area Apply up to three patches only once for up to 12 hours within a 24-hour period Patches may be cut into smaller sizes with scissors prior to removal of the release liner Clothing may be worn over the area of application Smaller areas of treatment are recommended in a debilitated patient or a patient with impaired elimination

If irritation or a burning sensation occurs during application, remove the patch(es) and do not reapply until the irritation subsides

When LIDODERM is used concomitantly with other products containing local anesthetic agents, the amount absorbed from all formulations must be considered

HANDLING AND DISPOSAL

Hands should be washed after the handling of LIDODERM and eye contact with LIDODERM should be avoided The used patch should be immediately disposed of in such a way as to prevent its access by children or pets

HOW SUPPLIED

LIDODERM (lidocaine patch 5%) is available as the following

NDC 63481-687-06 resealable envelope containing 5 patches (10 cm x 14 cm) box of 6 envelopes

KEEP ENVELOPE SEALED AT ALL TIMES WHEN NOT IN USE

Store at 25°C (77°F), excursions permitted to 15° 30°C (59°-86°F) [See USP Controlled Room Temperature]

Endo®

Manufactured for
Endo Pharmaceuticals Inc
Chadds Ford Pennsylvania 19317

Manufactured by
TEIKOKU SEIYAKU CO.,LTD
Sanbonmatsu Kagawa 769-2695
Japan

LIDODERM® is a Registered Trademark of Hind Health Care Inc

Printed in Japan

6524-01/March 1999

7-18-2005.

Endo Pharmaceutical, Inc.

Just three days ago a wonderful thing happened — Lidoderm came into my life.

For 26 years I've suffered from a very bad case of shingles followed by severe neuralgic pains and spasms ever so often.

I have used the patches three times now, and enjoying a nights rest, and the rest is a long time.

Dr Ronald Mac is my doctor, thanks to the samples from you folks, and prescriptions for more I can enjoy living again.

I have called all the doctors offices to tell them of my success, hoping to help others.

Just wanted to share the good news, keep up the good work and God bless.

(over)

Gratefully,

Thelma Rosewarne

July 12, 2000

Endo Pharmaceuticals, Inc.
Chadds Ford, Pa. 19317

Re: Lidoderm Patch

To Whom It May Concern:

In October 1997 I had cataract surgery and one of the followup medications was Profenal. After several days of using these drops I developed an allergic reaction (we discovered a cautionery note on the package that this sometimes happens) resulting in a severe case of shingles. My medical doctor prescribed everything for relief from topical to internal but to no avail. As time went on some of the pain lessened but the discomfort did not go away.

In September 1999 my niece read an article in a journal at her job in a hospital which described Lidoderm and lo and behold I have finally found relief (not a cure). At this point, I do not use it daily but when I awake with the recognizable distress, I use this product and within a short time I have relief.

I have thought of writing many times, but finally decided it was time to share my success. Thank you for this product and please pass my thanks on to Dr. Harry Hind whose address I could not find.

Very truly yours,

Ethel T. Reimer

Mrs. Ethel T. Reimer
345 Bullard Ave.
Paramus, N.J. 07652

P.S. When I showed my physician the article back in 1999, he had never heard of this product and we had to make several phone calls before finally locating it through AARP Pharmaceutical Dept. I have also mentioned it to several friends troubled as I was.

Frieda Krueger, Jackson Heights, New York

A particularly painful case of shingles and resulting postherpetic neuralgia (PHN) pain along her side left Frieda Krueger practically incapacitated Frieda, now 77, spent almost five years searching for some relief before trying the LIDODERM® patch (lidocaine patch 5%) in early 1999 She found the relief she was hoping for in the patch.

Previously, Frieda had tried almost every remedy available for the intense PHN pain she has across her left side. She saw internists, neurologists and anesthesiologists She tried various pain medications, acupuncture and epidurals She had an intrathecal pump implanted – it didn't work. She spent four days in New York University hospital trying various treatments Nothing worked and Frieda was miserable.

Frieda says, "no one can ever imagine how bad the pain was " For two years, she says she lay on the couch or in her bed She couldn't even get dressed or go on any outings Her husband used to push her outside in a wheelchair just to get some fresh air She describes her pain as an intense burning sensation, with "shots of electricity" running down her side.

Frieda finally found Dr Bradley Galer of Beth Israel Pain Center, one of the lead investigators for LIDODERM® Since starting to use the patch in January 1999, Frieda has gotten some real relief and is again "able to function." She goes on walks and to social engagements and enjoys being active again

6/99

Everett Asaro, South San Francisco, California

When asked to describe the nerve pain he experienced after a case of shingles, Everett Asaro says, "it was devastating, like a hot knife sticking in my back, twisting and turning "

Everett, now 78 years old, contracted shingles ten years ago and the pain from the damaged nerves across his back – postherpetic neuralgia (PHN) - has remained ever since. Everett was completely "knocked out" by the pain Any activity aggravated the nerves, so he ceased all activity. Any touch on his back, including clothes or even bedcovers, caused him such intense pain he would "jump out of (his) skin." When clothes were absolutely necessary, Everett would cut holes out of the back of his shirts so it didn't touch the painful area

Everett, a retired butcher, tried oral pain medications, cold packs and hot packs. Nothing worked on his pain. Everett then read in the newspaper about the clinical trials for LIDODERM® (lidocaine patch 5%) that were taking place at the University of California, San Francisco He says he feels very fortunate that he was accepted into the program, because the patches work "beautifully" to control his pain Everett says he doesn't know what he'd do without LIDODERM®

Everett wears a patch every day He is playing golf again, and is enjoying spending time relatively pain-free with his wife, 4 children, 12 grandchildren and 6 great-grandchildren

6/99

Phyllis Bohanon, Portland, Oregon

When Phyllis Bohanon, now age 71, was being treated with chemotherapy for breast cancer in 1985, the last thing on her mind was the shingles virus. However, on top of everything else she was dealing with, Phyllis contracted a painful case of shingles, a reactivation of the chicken pox virus that most often attacks people whose immune systems are weakened, such as the elderly, AIDS patients or patients undergoing chemotherapy.

The shingles rash broke out across her back on her spine and around her arm And, unfortunately for Phyllis, she experienced permanent nerve damage. She says the shooting pain across her back and arm was "horrible and unbearable."

Phyllis was an x-ray technician who had returned to college in her 50s She had raised five children and was an avid gardener. When her postherpetic neuralgia (PHN) pain was at its worst, Phyllis would do nothing more than "sit in a chair, hardly moving." She tried oral pain medications, which she said didn't do anything to control her pain. She also tried TENS (transcutaneous electrical nerve stimulation), with no relief

Phyllis heard from a neighbor about a new PHN study that was to take place in Seattle She was accepted into the trial and left for Seattle hopeful The LIDODERM® patch (lidocaine patch 5%) worked to control her pain and Phyllis is thrilled

Phyllis uses three patches a day, every day, combining them with some prescription pain medication when she knows she is going to be particularly active She does volunteer work at her church, and tutors school children She is also back to her gardening and is enjoying some extensive traveling with her husband and family

6/99

Joseph Wahed, San Francisco, California

Joseph Wahed, 63, says that he spent months at a time "virtually a prisoner in (his) own house," due to the intense nerve pain he experienced after a case of shingles Joe's shingles outbreak in 1992 was across his back and right side. He describes the constant postherpetic neuralgia (PHN) pain that followed as excruciating, saying that even someone blowing on his back or wind could cause him agony. He could not have anything touch his back and didn't wear a shirt for months at a time.

An avid golfer and tennis player, Joe had to give up the activities he enjoyed He also couldn't work for a time at his job as a chief economist for Wells Fargo Bank.

Joe tried all available methods to get some pain relief. Strong oral pain medications helped a little, but he says, they caused drowsiness, lethargy, constipation and impaired judgement. And the medications lost their effectiveness over time. Joe also tried antidepressants, anticonvulsants, injections along the nerves on his back, and acupuncture. Desperate to get his life back, he saw medical doctors, chiropractors and even what he calls a "witch doctor "

Dr Michael Rowbotham of the University of San Francisco Pain Center enrolled Joe in the first set of clinical trials for the LIDODERM® patch (lidocaine patch 5%) Joe says that from the minute he put the patch on, he got true relief from his pain for the first time, without any side effects He calls the patch a "wonderful, wonderful invention "

Joe is active again and enjoying life. He is also looking forward to his younger son's upcoming wedding, which he believes he would not even be able to attend without LIDODERM®

6/99

Mary Conover, Redmond, Washington

"If I can just live through December, maybe things will get better," 77-year-old Mary Conover remembers thinking in the summer of 1992, when she was stricken by postherpetic neuralgia (PHN) pain after a case of shingles.

Mary's nerve damage is on her upper arm, in her armpit and across her back. The pain is "non-stop, excruciating and indescribable," she says. She was in such pain that she had to give up all the activities she enjoyed, including jazzercize classes and rugbraiding

Her family doctor diagnosed the PHN and attempted to treat her pain with a variety of products Mary recalls nasty side effects from oral pain medications and antidepressants that didn't work on her pain. She tried bee sting therapy and even had a lidocaine infusion. Nothing helped

Mary then participated in the LIDODERM® (lidocaine patch 5%) study at the University of Washington. The patch, says Mary, is "a howling success." She feels the patches, which she uses every day, have completely changed her life. "It's like night and day," she says Mary's husband, two daughters and three grandchildren confer – they are thrilled to have the old Mary back.

6/99

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June 29, 1999

BY FACSIMILE/CONFIRMATION COPY BY MAIL

Ms Laura E W Noble
Compliance Officer
Office of Compliance
Chemicals, Clothing, and Household Products Team
U S Consumer Product Safety Commission
4330 East-West Highway
Bethesda, Maryland 20814

Dear Ms Noble

This confirms and expands on our telephone conversation of June 22, 1999 concerning the Commission's letter of June 14, 1999 to Endo Pharmaceuticals, Inc ("Endo") Endo, the marketer of Lidoderm® (lidocaine patch 5%), has asked us to represent the company in this matter.

The Commission's letter refers to the "final rule requiring child-resistant packaging for products containing lidocaine," codified at 16 C F R. § 1700.14(a)(23), and promulgated under the authority of the Poison Prevention Packaging Act (PPPA). The Commission's letter also alleges that "if the *Lidoderm* packaging does not comply with the PPPA, it will be a misbranded drug as defined by section 502(p) of the Federal food, Drug, and Cosmetic (FD&C) Act."

Briefly, Endo's position is that the lidocaine standard at 16 C F R. § 1700 14(a)(23) does not apply to lidocaine products in patch form ("lidocaine patches"), and that the Commission does not have the statutory authority to enforce the standard against lidocaine patches.

I. FAILURE TO MAKE REQUISITE FINDINGS FOR LIDOCAINE PATCHES

For lidocaine patches, the Commission has not made any of the findings required by the PPPA to impose a standard As the Commission itself admits in the preamble to the final rule for "products containing lidocaine"

> The . .PPA . authorizes the Commission to establish standards for the "special packaging" of any household substance if . the special packaging is technically feasible, practicable, and appropriate for such substance
>
> The findings that the Commission **must make in order to issue a standard** requiring child-resistant . . packaging for a product are discussed below in Section E [1]

Section E of the preamble to the final rule repeats that

> the Commission **is required by** section 3(a)(2) of **the PPPA to find** that the special packaging is "technically feasible, practicable, and appropriate "[2]

Moreover, the PPPA also requires the commission to find that "the degree or nature of the hazard to children in the availability of such substance, by reason of its packaging, is such that special packaging is required to protect children "[3] It is clear that the Commission

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1 60 Fed Reg. 17992, 17993 (April 10, 1995) (emphasis added).

2 Id at 18002 (emphasis added) "Technical feasibility" exists when the technology exists or readily can be developed and implemented by the effective date to produce packaging conforming to the standard. Id. "Practicability" means that special packaging complying with the standard can utilize modern mass production and assembly line techniques. Id. "Appropriateness" exists when packaging complying with the standard will adequately protect the integrity of the substance and not interfere with the intended storage or use Id

3 15 U S C § 1472(a)(1) (emphasis added)

cannot make the findings required by the PPPA without considering the dosage forms and the packaging used for products containing the substance

The notice of proposed rulemaking[4] and the final rule reflect that the Commission made the required findings only with respect to (1) the following dosage forms "creams, ointments, gels, jellies, viscous solutions, liquids, sprays, aerosols, and injectables," and (2) the following types of packaging: "tube packaging," "squeeze or pump bottles," and "aerosol sprays "[5] The Commission considered also prefilled syringes and a product "in a foil packet containing 1/8 oz of gel."[6]

In order for the standard to legally apply to lidocaine patches, the Commission must make the following findings:

- That the hazard to children in the availability of lidocaine, by reason of its being in a patch, is such that special packaging is required.
- That the technology exists or readily can be developed and implemented by the effective date to produce lidocaine patches packaging conforming to the standard.
- That, for lidocaine patches, special packaging complying with the standard can utilize mass production and assembly techniques.
- That special packaging complying with the standard will adequately protect the integrity of lidocaine in a patch and not interfere with the product's intended storage or use.

For lidocaine in patches, the Commission did not make any of the findings required by the PPPA Therefore, (1) the standard cannot be interpreted to apply to lidocaine patches, (2) the Commission does not have statutory authority to enforce the standard against lidocaine patches; and (3) Endo's Lidoderm® is not misbranded under section 502(p) of the FD&C Act

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4 57 Fed Reg. 34274 (Aug. 4, 1992).

5 See, e g., 60 Fed. Reg. at 17993-94, 18002-03

6 Id at 17994, 18001.

II. NO OPPORTUNITY FOR COMMENT

The Commission may not enforce the standard against lidocaine patches because interested parties were not given notice and an opportunity to comment on it. The PPPA provides that "[p]roceedings to issue, amend, or repeal . a standard . . shall be conducted in accordance with the procedures described by section 553 . of Title 5 [i e., the Administrative Procedure Act (APA)] . . . [7] The APA provides that a notice of proposed rulemaking shall include "either the terms or substance of the proposed rule or a description of the subjects and issues involved "[8] Furthermore, the APA provides that, "[a]fter notice required by this section, the agency shall give interested persons an opportunity to participate in the rule making through submission of written data, views, or arguments with or without opportunity for oral presentation."[9]

Neither the notice of proposed rulemaking nor the final rule contained any indication that the standard could apply to lidocaine patches To the contrary, the detailed and specific discussions concerning types of dosage forms and packaging for lidocaine—which fail to make any reference to patches—would reasonably and logically lead the public to conclude that the regulation was not intended to apply to lidocaine patches Endo and the public were not given notice that the standard might apply to lidocaine patches. Accordingly, there was never a true opportunity to comment on this issue in the rulemaking

With respect to its applicability to lidocaine patches, the regulation imposing the standard was not promulgated in accordance with the APA Therefore, the standard is invalid when applied to lidocaine patches

III. ENDO'S PRIOR COMMUNICATIONS WITH COMMISSION PERSONNEL

In December of 1998, Endo asked us to investigate the applicability of the standard to lidocaine patches On December 10, 1998, we discussed this issue with Dr Suzanne Barone, who was represented to us as the Commission's contact for the child-resistant packaging regulations

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7 15 U.S C § 1474(a).

8 5 U S C § 553(b)(3).

9 5 U S C § 553(c)

Dr. Barone informed us that the standard for lidocaine products was not intended to apply to lidocaine patches simply because they were not on the market at the time the standard was proposed and finalized. Dr. Barone added that the Commission was "in the process of formulating its policy on patch products "

Thus, even after consulting with Commission staff, Endo had no reason to believe that the standard would apply to lidocaine patches. To the extent that the letter to Endo means that the Commission has now established a "policy" on lidocaine patches, the prior discussions in this letter make it clear that the Commission may not make a standard applicable to a class of products simply by adopting a "policy " There must be a rulemaking proceeding that affords interested parties the opportunity to comment, and in which the Commission makes the findings required by the PPPA to impose a standard

IV. APPLYING STANDARD TO LIDODERM® COULD HAVE SEVERE ADVERSE EFFECT ON AVAILABILITY OF AN ORPHAN DRUG

On October 24, 1995, the Food and Drug Administration (FDA) designated Lidoderm® as an "orphan drug" (see Attachment 1) [10] An orphan drug is a drug intended to treat a rare condition that affects fewer than 200,000 persons in the U S , or affects more than 200,000 persons but for which there is no reasonable expectation that the cost of developing and making available the drug will be recovered from sales [11] The orphan drug provisions of the FD&C Act are intended to encourage the development and marketing of drugs for rare diseases, through the use of certain economic incentives.[12] Without these economic incentives, the rare condition would go untreated with drugs See Attachment 3

To require Endo to now halt the launch of this orphan drug while it attempts to find child-resistant packaging, and determine whether such packaging is "appropriate" for Lidoderm®, would further delay the availability of therapy for persons suffering from this rare condition In addition, Endo would need to determine whether the increased cost of using child-resistant packaging would make the product so unprofitable as to negate the incentives in the FD&C Act.

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10 Approval to market Lidoderm® was not granted until March 19, 1999 (see Attachment 2)

11 21 U S C § 360bb(a)(2)

12 See, e g , 21 U.S C. § 360cc

Finally, Endo wishes to point out that the envelope in which the Lidoderm® patches are contained bears the following warning. "WARNING. Package not child resistant Keep used and unused patches out of the reach of children and pets."

V. CONCLUSION

Expanding the scope of the standard for lidocaine products to include lidocaine patches is in violation of the PPPA, the APA, and the Commission's regulations (16 C F R § 1700.3) The Commission has no statutory authority to enforce the standard against lidocaine patches.

In addition to being contrary to the applicable statutes, it would be wholly unfair for the Commission to attempt to enforce the standard against lidocaine patches without first engaging in appropriate rulemaking. If the Commission wishes to make the regulation applicable to lidocaine patches, it should publish a notice of proposed rulemaking Interested members of the public, including the industry, should be provided an opportunity to comment We assure the Commission that Endo will participate fully in any new rulemaking

Please do not hesitate to contact us if you need additional information or wish to discuss this matter

Sincerely,

HYMAN, PHELPS & McNAMARA, P C
Counsel for Endo Pharmaceuticals, Inc

Samia N. Rodriguez
By Samia N Rodriguez

SNR/slk

LIST OF ORPHAN PRODUCTS DESIGNATIONS AND APPROVALS

Through December 31, 1998

NAME Generic Name TN=Trade Name	INDICATION DESIGNATED	SPONSOR & ADDRESS DD=Date Designated MA=Marketing Approval
Levocarnitine TN= Carnitor	Treatment of zidovudine-induced mitochondrial myopathy	Sigma-Tau Pharmaceuticals, Inc. 800 S. Frederick Avenue, Suite 300 Gaithersburg, MD 20877 DD=04/07/1997 MA= / /
Levomethadyl acetate hydrochloride TN= Orlaam	Treatment of heroin addicts suitable for maintenance on opiate agonists	Biodevelopment Corporation 8180 Greensboro Drive, Suite 1000 McLean, VA 22102 DD=01/24/1984 MA=07/09/1993
Lidocaine patch 5% TN= Lidoderm Patch	For relief of allodynia (painful hypersensitivity), and chronic pain in post-herpetic neuralgia.	Hind Health Care, Inc. 3707 Williams Rd., Suite 101 San Jose, CA 95117 DD=10/24/1995 MA= / /
Liothyronine sodium injection TN= Triostat	Treatment of myxedema coma/precoma.	SmithKline Beecham Pharmaceuticals One Franklin Plaza P O Box 7929 Philadelphia, PA 19101 DD=07/30/1990 MA=12/31/1991
Lipid/DNA human cystic fibrosis gene TN=	Treatment of cystic fibrosis	Genzyme Corporation P O Box 9322 One Mountain Road Framingham, MA 01701 DD=04/08/1996 MA= / /
Liposomal Cyclosporin A TN= Cyclospire	For aerosolized administration in the prevention and treatment of lung allograft rejection and pulmonary rejection events associated with bone marrow transplantation.	Vernon Knight, M.D Baylor College of Medicine, Dept. of Molecular Physiology One Baylor Plaza Houston, TX 77030 DD=04/30/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of osteosarcoma.	Endorex Corp 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of Ewing's sarcoma.	Endorex Corp 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal amphotericin B TN= AmBisome	Treatment of cryptococcal meningitis	Fujisawa USA, Inc 3 Parkway North Center Deerfield, IL 60015 DD=12/10/1996 MA=08/11/1997

LAMIVUDINE

SOLUTION, ORAL
EPIVIR-HBV
+ GLAXO WELLCOME 5MG/ML N21004 001 DEC 08, 1998
+ 5MG/ML N20596 002 DEC 08, 1998

TABLET, ORAL
EPIVIR-HBV
+ GLAXO WELLCOME 100MG N21003 001 DEC 08, 1998
+ 100MG N20564 002 DEC 08, 1998

LEUCOVORIN CALCIUM

INJECTABLE, INJECTION
LEUCOVORIN CALCIUM
AP + ABBOTT EQ 10MG BASE/ML N40147 001 JUN 25, 1997
AP + BEDFORD EQ 200MG BASE/VIAL N40056 001 MAY 23, 1995

LEUCOVORIN CALCIUM PRESERVATIVE FREE
AP + ABBOTT EQ 10MG BASE/ML N40147 001 JUN 25, 1997
AP + BEDFORD EQ 200MG BASE/VIAL N40056 001 MAY 23, 1995
AP BIGMAR EQ 10MG BASE/ML N40286 001 FEB 26, 1999
AP EQ 200MG BASE/VIAL N40258 001 FEB 26, 1999

TABLET, ORAL
LEUCOVORIN CALCIUM
> ADD > AB INVAMED EQ 15MG BASE N75327 001 MAR 24, 1999

> ADD > LEVALBUTEROL HYDROCHLORIDE

> ADD > SOLUTION, INHALATION
> ADD > XOPENEX
> ADD > + SEPRACOR EQ 0 021% BASE N20837 001 MAR 25, 1999
> ADD > + EQ 0 042% BASE N20837 002 MAR 25, 1999

LIDOCAINE

> ADD > FILM, EXTENDED RELEASE, TRANSDERMAL
> ADD > LIDODERM
> ADD > + HIND HLTHCARE 700MG/12HR N20612 001 MAR 19 1999

LIDOCAINE, PRILOCAINE

AEROSOL, TOPICAL
EMLA
+ ASTRA PHARMS 2 5%;2 5% N20962 001 FEB 04, 1998

DISC, TOPICAL
EMLA
+ ASTRA PHARMS 2 5% 2 5% N20962 001 FEB 04 1998

LISINOPRIL

TABLET ORAL
ZESTRIL
ZENECA 30MG N19777 00[illegible] JAN 26 1[illegible]

LITHIUM CARBONATE

CAPSULE, ORAL
LITHONATE
AB SOLVAY 300MG N16782 00
300MG N16782 00

TABLET ORAL
LITHIUM CARBONATE
AB PFIZER 300MG N16834 00
AB + 300MG N16834 00
LITHOTABS
AB + SOLVAY 300MG N16980 00
300MG N16980 00

MEPERIDINE HYDROCHLORIDE

INJECTABLE, INJECTION
DEMEROL
AP + ABBOTT 25MG/ML N05010 0[illegible]

LAMIVUDINE

SOLUTION, ORAL
EPIVIR-HBV
+ GLAXO WELLCOME — 5MG/ML — N21004 001 DEC 08, 1998
+ — 5MG/ML — N20596 002 DEC 08, 1998

TABLET, ORAL
EPIVIR-HBV
+ GLAXO WELLCOME — 100MG — N21003 001 DEC 08, 1998
+ — 100MG — N20564 002 DEC 08 1998

LEUCOVORIN CALCIUM

INJECTABLE, INJECTION
LEUCOVORIN CALCIUM
AP + ABBOTT — EQ 10MG BASE/ML — N40147 001 JUN 25, 1997
AP + BEDFORD — EQ 200MG BASE/VIAL — N40056 001 MAY 23, 1995

LEUCOVORIN CALCIUM PRESERVATIVE FREE
AP + ABBOTT — EQ 10MG BASE/ML — N40147 001 JUN 25, 1997
AP + BEDFORD — EQ 200MG BASE/VIAL — N40056 001 MAY 23, 1995
AP BIGMAR — EQ 10MG BASE/ML — N40286 001 FEB 26, 1999
AP — EQ 200MG BASE/VIAL — N40258 001 FEB 26 1999

TABLET, ORAL
LEUCOVORIN CALCIUM
> ADD > AB INVAMED — EQ 15MG BASE — N75327 001 MAR 24, 1999
> ADD >

> ADD > LEVALBUTEROL HYDROCHLORIDE

> ADD > SOLUTION, INHALATION
> ADD > XOPENEX
> ADD > + SEPRACOR — EQ 0 021% BASE — N20837 001 MAR 25, 1999
> ADD > + — EQ 0 042% BASE — N20837 002 MAR 25, 1999
> ADD >

LIDOCAINE

> ADD > FILM, EXTENDED RELEASE, TRANSDERMAL
> ADD > LIDODERM
> ADD > + HIND HLTHCARE — 700MG/12HR — N20612 001 MAR 19, 1999
> ADD >

LIDOCAINE, PRILOCAINE

AEROSOL; TOPICAL
EMLA
+ ASTRA PHARMS — 2 5%;2 5% — N20962 001 FEB 04, 1998

DISC, TOPICAL
EMLA
+ ASTRA PHARMS — 2 5%,2 5% — N20962 001 FEB 04 1998

LISINOPRIL

TABLET, ORAL
ZESTRIL
ZENECA — 10MG — N19777 001 JAN 26 199

LITHIUM CARBONATE

CAPSULE ORAL
LITHONATE
AB SOLVAY — 300MG — N16782 00
— 300MG — N16782 00

TABLET, ORAL
LITHIUM CARBONATE
AB PFIZER — 300MG — N16834 00
AB + — 300MG — N16834 00
LITHOTABS
AB + SOLVAY — 300MG — N16980 00
— 300MG — N16980 00

MEPERIDINE HYDROCHLORIDE

INJECTABLE, INJECTION
DEMEROL
AP + ABBOTT — 25MG/ML — N05010 0

information regardless of the size of the proposed target patient population A product may still be designated as an orphan by demonstrating that the financial criteria of the law are applicable, regardless of the number of patients affected

P L 100-290 amended the Orphan Drug Act on April 18, 1988, and requires that the application for designation be made prior to the submission of an application for marketing approval, New Drug Application (NDA) or Product License Application (PLA) Prior to this amendment, the designation request could be filed at any time prior to FDA's approval to market the product

Section 1205 of P L 104-188 reinstated the tax credits for clinical testing expenses of orphan drugs for the period July 1, 1996 to May 31, 1997 and allows these credits to be carried forward/back like some other business tax credits.

The Orphan Drug Final Regulations were published in the Federal Register on December 29, 1992, and became effective thirty days thereafter

Orphan Drug Designation

In order for a sponsor to obtain orphan designation for a drug or biological product, an application must be submitted to OOPD, and the designation approved The approval of an application for orphan designation is based upon the information submitted by the sponsor A drug that has obtained orphan designation is said to have "orphan status " Each designation request must stand on its own merit Sponsors requesting designation of the same drug for the same indication as a previously designated product must submit their own data in support of their designation request The approval of an orphan designation request does not alter the standard regulatory requirements and process for obtaining marketing approval Safety and efficacy of a compound must be established through adequate and well-controlled studies

Incentives of the Orphan Drug Act

The Orphan Drug Act (P L 97-414, as amended) includes various incentives that have stimulated a considerable amount of interest in the development of orphan drug and biological products These incentives include tax credits for clinical research undertaken by a sponsor to generate required data for marketing approval, and seven years of marketing exclusivity for a designated drug or biological product approved by the FDA

Section 527 of the Orphan Drug Act provides a seven-year period of exclusive marketing to the first sponsor who obtains marketing approval for a designated orphan drug or biological product Exclusivity begins on the date that the marketing application is approved by FDA for the designated orphan drug, and applies only to the indication for which the drug has been designated and approved A second application for the same drug for a different use could be approved by FDA.

Final regulations on the tax credits were published in the Federal Register on October 3, 1988 (53 FR 38708), and the current version of these regulations are in Title 26, Code of Federal Regulations, Section 45c The Internal Revenue Service administers the tax credit provisions, and specific questions about the interpretation of the law or regulations affecting the applicability of the tax credit provision of the Act should be directed to IRS If more information on tax credits is needed, contact Pass Through and Special Industries Division, Office of the Chief Counsel, Internal Revenue Service, 1111 Constitution Avenue, NW, Washington, DC 20224, telephone is (202) 622-3120

Protocol Assistance

Section 525 of the Orphan Drug Act provides for formal protocol assistance when requested by the sponsors of drugs for rare diseases or conditions The formal review of a request for protocol assistance is the direct responsibility of the Center for Drug Evaluation and Research (CDER) or the Center for Biologic Evaluation and Research (CBER), depending on which Center has authority for review of the product The Office of Orphan Products Development (OOPD) is responsible for insuring that the request qualifies for consideration under section 525 of the FFDCA. This includes determining "whether there is reason to believe the sponsor's drug is a drug for a disease or condition that is rare in the United States " A sponsor need not have obtained orphan drug designation to receive protocol assistance.

Once OOPD determines that the proposed compound is for a disease or condition that is rare in the U S , the request will be forwarded to the responsible reviewing division for formal review and direct response OOPD monitors the review process within the respective CDER/CBER reviewing division and, where possible, assists in resolving specific issues that may arise during the review process It should be understood that protocol assistance provided under the Act does not waive the necessity for the submission of an Investigational New Drug Application (IND) by sponsors planning to conduct clinical trials with the product

Research Grants

The FDA, through OOPD, funds the development of orphan products through its grants program for clinical studies The Request for Applications (RFA) announcing availability of funds is published in the Federal Register each year - usually in June Eligibility for grant funding is extended to medical devices and medical foods for which there is no reasonable expectation of development without such assistance Applications are reviewed by panels of outside experts and are funded by priority score

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September 7, 1999

BY FACSIMILE/CONFIRMATION COPY BY HAND

Ms Laura E W Noble
Compliance Officer
Office of Compliance
Chemicals, Clothing, and Household Products Team
U S Consumer Product Safety Commission
4330 East-West Highway
Bethesda, Maryland 20814

Dear Ms Noble

This responds to the Commission's letter of August 19, 1999, concerning Lidoderm®, a prescription orphan drug in patch form to be marketed by Endo Pharmaceuticals, Inc ("Endo").

The Commission's August 19th letter only confirms the importance of the requirement of the Poison Prevention Packaging Act (PPPA) that the Commission issue a special packaging standard (a) "by regulation," (b) after "it finds that . the special packaging to be required by such standard is technically feasible, practicable, and appropriate," (c) after considering its reasonableness, available scientific, medical, and engineering data concerning the special packaging, the manufacturing practices of the industries affected, and the nature and use of the household substance, and (d) if it "publishes" its findings and reasons therefor 15 U S.C § 1472(a)-(c). See also 16 C F R. § 1700 3.

Endo reiterates that, with respect to its applicability to lidocaine patches, and Endo's product in particular, the standard at 16 C.F R. § 1700 14(a)(23) was not promulgated in compliance with the requirements of the PPPA, the Administrative Procedure Act (APA), and the agency's own regulations Therefore, the Commission does not have the statutory authority to enforce the standard against Endo's lidocaine patch

First Point in Letter

The first point in the August 19th letter is that "there was ample opportunity for all interested parties to comment upon this proposed rule "

Endo is not asserting that there was no "ample opportunity" to comment Endo's position is that there was no opportunity for lidocaine patch marketers to comment because they were not "interested parties " Notice "must provide sufficient factual detail and rationale for the rule to permit interested parties to comment meaningfully " Florida Power & Light Co v United States, 846 F 2d 765, 771 (D C Cir 1988) (emphasis added), see also American Medical Ass'n v Reno, 57 F 3d 1129, 1132 (D C Cir 1995) The only lidocaine "patches" approved by the Food and Drug Administration (FDA) for marketing are Endo's patch and the Emla disc (see Attachment 2 to our letter of June 29, 1999) These products were not being marketed at the time the standard was promulgated. The Emla disc was not approved for marketing until February 4, 1998 Id Endo's product was approved for marketing on March 19, 1999 Id FDA did not even designate Lidoderm® as an orphan drug (this does not authorize marketing) until October 24, 1995, more than six months after the Commission published the final rule See Attachment 1 to our letter of June 29, 1999

Thus, today's marketers of lidocaine "patches," including Endo, were not "interested parties" when the standard was promulgated. If they were not "interested parties," they cannot be deemed to have received notice and an opportunity to comment meaningfully Indeed, they had no opportunity at all to comment.

The APA provides that a reviewing court may "hold unlawful and set aside agency action ... found to be . without observance of procedure required by law " 5 U S C § 706(2)(D) An agency's failure to use notice-and-comment rulemaking is subject to "strict scrutiny" by a reviewing court. Environmental Defense Fund, Inc v Gorsuch, 713 F 2d 802, 816-17 (D C Cir. 1983) ("Any claim of exemption from APA rulemaking requirements 'will be narrowly construed and only reluctantly countenanced '"), Natural Resources Defense Council, Inc v EPA, 683 F 2d 752, 760 (3d Cir 1982) ("'[R]eview of an agency's procedural compliance with statutory norms is an exacting one.' *NRDC v SEC*, 606 F 2d 1031, 1048 (D.C Cir 1979). The exacting standard applicable in

determining whether an agency has failed to comply with the procedural requirements for its action contrasts with the deferential standard applicable to substantive challenges to agency action.").

The Commission's regulations set forth the PPPA's requirements for establishing a special packaging standard, and confirm that such agency action "shall be in accordance with section 5 of the [PPPA] as to procedure." 16 C.F R. § 1700 3 Section 5 of the PPPA, 15 U S C. § 1474(a), requires the Commission to use the notice-and-comment procedure of section 553 of the APA, 5 U.S.C § 553(b)(3). It is a well-established principle that agencies must follow their own regulations Vitarelli v Seaton, 369 U S 535, 545 (1959); Service v Dulles, 354 U.S 363, 388 (1957), Saddler v Department of Army, 68 F 3d 1357, 1358 (Fed. Cir 1995)

Where an agency fails to abide by its own regulations, a reviewing court should set the resulting agency action aside Kelly v Railroad Retirement Bd , 625 F.2d 486, 492 (3d Cir. 1980) ("[f]ailure to comply with its regulations renders the agency's act null"), Union of Concerned Scientists v Atomic Energy Comm'n, 499 F 2d 1069, 1082 (D C Cir 1974) ("an agency's failure to follow its own regulations is fatal to the deviant action"), Doyle v Brock, 632 F Supp 256, 263 (D D C. 1986) ("[a]gency action inconsistent with the regulations must be overturned"), aff'd, 821 F 2d 778 (D C Cir 1987) The D C Circuit has said it very eloquently.

> [I]t is elementary that an agency must adhere to its own rules and regulations *Ad hoc* departures from those rules, even to achieve laudable aims, cannot be sanctioned . for therein lie the seeds of destruction of the orderliness and predictability which are the hallmarks of lawful administrative action

Reuters Ltd v FCC, 781 F 2d 946, 950-51 (D C Cir 1986)

Second Point in Letter

The second point in the August 19th letter is that the regulation "is quite clear" because it mentions "products containing lidocaine" without any qualification other than the amount of lidocaine.

This agency statement ignores the context in which the regulation was promulgated and dismisses the fact-finding requirements of the PPPA. Regardless of the "clarity" of a regulation, it will not be valid if it is not consistent with the statute under which it was promulgated. See, e g., United States v Larionoff, 97 S Ct. 2150, 2156 (1977), Webb v Hodel, 878 F 2d 1252, 1255 (10th Cir 1989)

Third Point in Letter

The third point in the August 19th letter is that "it is apparent that the Commission intended to include all delivery systems ... including lidocaine-containing patches " The support given for this allegation is that comments were filed seeking exclusion of some dosage forms but the Commission "expressly determined that the rule should not exempt certain products because [of] the potential for injury "

First, this simply shows that the Commission did not refuse to exempt lidocaine patches because no comments mentioning lidocaine patches were filed or could have been filed. Second, a "potential for injury" is only one of the findings the Commission is required to make Thus, even assuming, for the sake of argument, that the Commission made a finding that lidocaine patches had a "potential for injury," that would not make the standard legally applicable to such products because the other required findings were not made for lidocaine patches Moreover, the degree or nature of the hazard of a substance to children must be assessed "by reason of its packaging " 15 U S C § 1472(a)(1) (emphasis added) The Commission did not consider lidocaine-patch "packaging," as required by the PPPA and its own regulations.

The "all delivery systems" that the commission "intended to include" were the delivery systems being marketed at that time. To the extent that the Commission believes that it may apply a special packaging standard to any and all new delivery systems that come into the market after the standard is promulgated, the provisions of the PPPA do not support that position. The PPPA requires the Commission to make special packaging findings based on the "packaging" for the product

Finally, it simply flies in the face of logic to contend that the Commission "intended" to include a delivery system that did not exist at the time the regulation was promulgated One cannot "intend" to do that about which one has no knowledge

Fourth Point in Letter

The fourth point in the August 19th letter is that because "there are lidocaine patches currently ... in child-resistant packaging," it "is evident that it is technically feasible, practicable, and appropriate for lidocaine patches to be in child-resistant packaging " The letter also states that "lidocaine's action occurs through topical application to the affected area."

First, the PPPA does not allow the Commission to establish a standard simply by stating in a letter to one company that "it is evident" that the special packaging is technically feasible, practicable, and appropriate The law requires the Commission to

make this and other specific findings by notice-and-comment rulemaking. The PPPA and APA's requirements are intended to ensure agency compliance with the Due Process Clause of the Constitution of the United States Surely the Commission is not asserting that the Constitution has no bearing on its activities

Second, Endo's product is not a topical product—it is a transdermal, extended release patch that does not function as a topical product. The FDA-approved package insert for Lidoderm® (copy attached) states

> The penetration of lidocaine into intact skin after application of LIDODERM® is sufficient to produce an analgesic effect, but less than the amount necessary to produce a complete sensory block.

Unlike other lidocaine products, Lidoderm® does not work by having a topical anesthetic effect—Lidoderm® has a transdermal, analgesic, localized effect, for the relief of pain associated with post-herpetic neuralgia, which is a rare condition in the U S As a result, what might be feasible, practicable, and appropriate for other lidocaine products is not necessarily feasible, practicable, and appropriate for Endo's lidocaine patch This agency statement is evidence of the perils involved when an agency takes regulatory action without following the required due process requirements imposed by Congress and the Constitution

For an agency regulation to survive an "arbitrary and capricious" analysis, the agency must, at a minimum, "examine the relevant data and articulate a satisfactory explanation for its action including a 'rational connection between the facts found and the choice made '" Motor Vehicle Manufacturers Ass'n of the United States v State Farm Mutual Automobile Insurance Co , 463 U S , 29, 43 (1983) (emphasis added) (quoting Burlington Truck Lines, Inc v United States, 371 U S 156, 158 (1962)) In this case, the Commission cannot say that application of the standard to Endo's product is not arbitrary and capricious It is impossible for the Commission to assert that there is a "rational connection between the facts found and the choice made" because the Commission has made no findings at all for lidocaine patches such as Endo's product

Also, "[i]n addition to requiring a reasoned basis for agency action, the 'arbitrary or capricious' standard requires an agency's action to be supported by the facts in the record " Olenhouse v Commodity Credit Corp , 42 F 3d 1560, 1575 (10th Cir. 1994) (emphasis added). Here, with the possible exception of the findings relating to lidocaine's toxicity (which is only one of the issues the Commission is required to address), there are no findings in the rulemaking record that support the Commission's position that the standard applies to Endo's product.

imposed on a product simply because the marketer is aware that there are toxicity hazards Even assuming that such awareness is relevant when the Commission makes a hazard determination, it would not be sufficient to cover all of the findings that the PPPA requires the Commission to make. The PPPA requires that the Commission make the toxicity hazard finding by notice-and-comment rulemaking and considering the packaging for the product. This the Commission has failed to do for lidocaine patches.

Second, Endo is not using the warning to comply with the standard because the standard does not apply to Endo's product

Conclusion

The Commission's regulation for lidocaine products, as applied to lidocaine patches such as Endo's, was not promulgated in accordance with the requirements of the PPPA, the APA, and the Commission's regulations Because lidocaine patches were not considered by the Commission at the time the rule was issued, and could not have been considered because they were not being marketed at that time, Endo's product is not subject to the standard for lidocaine products.

Final Remarks

We are appalled at the Commission's nonchalant dismissal of the requirements of the PPPA. The Commission's response to our June 29, 1999 letter completely ignores Endo's legal arguments. Briefly summarized, the Commission's position is that the standard applies to Endo's product because (1) the Commission promulgated a standard for "products containing lidocaine," and (2) although lidocaine patches did not exist at the time the standard was promulgated, it is desirable to apply the standard to such products because they may present a safety hazard to children The agency has chosen to ignore that, under the principles of administrative law, the standard may not be legally applied to lidocaine patches simply because the agency considers it a laudable thing to do No reviewing court will countenance an agency's failure to comply with the procedural and substantive requirements imposed upon it, however convenient and efficient such failure might be

Endo will vigorously defend its product against any attempts to enforce the standard against it. Any such enforcement attempt would not be lawful because it would be based on an invalid/misinterpreted regulation See, e g , Aerolineas Argentinas v United States, 77 F 3d 1564, 1574-76, 1578 (Fed Cir. 1996)

Endo's failure to make the product available could result in its losing orphan drug marketing exclusivity under the Federal Food, Drug, and Cosmetic Act (FDC Act) During

the seven years following marketing approval, orphan drug marketers must "assure the availability of sufficient quantities of the drug to meet the needs of persons with the disease or condition for which the drug" was approved. 21 U.S C § 360cc(b)(1) Also, since the product was approved in March, Endo has received well over 3,000 calls from sufferers of post-herpetic neuralgia asking when the only FDA-approved drug for their condition will be available to ease their pain and suffering In order to meet the requirements of the FDC Act and the serious needs of these patients, Endo cannot delay the launch of the product

Sincerely,

HYMAN, PHELPS & McNAMARA, P C.
Counsel for Endo Pharmaceuticals, Inc

By Samia N Rodriguez

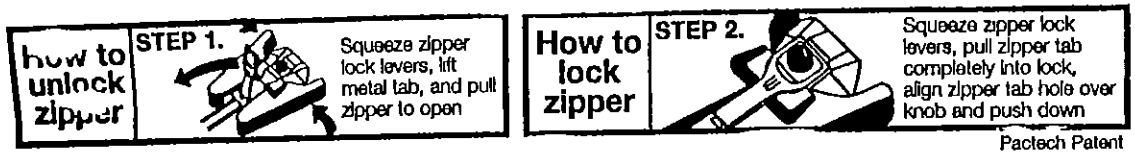
SNR/tee

Attachment

LIST OF ORPHAN PRODUCTS DESIGNATIONS AND APPROVALS

Through December 31, 1998

NAME Generic Name TN=Trade Name	INDICATION DESIGNATED	SPONSOR & ADDRESS DD=Date Designated MA=Marketing Approval
Levocarnitine TN= Carnitor	Treatment of zidovudine-induced mitochondrial myopathy.	Sigma-Tau Pharmaceuticals, Inc. 800 S Frederick Avenue, Suite 300 Gaithersburg, MD 20877 DD=04/07/1997 MA= / /
Levomethadyl acetate hydrochloride TN= Orlaam	Treatment of heroin addicts suitable for maintenance on opiate agonists.	Biodevelopment Corporation 8180 Greensboro Drive, Suite 1000 McLean, VA 22102 DD=01/24/1984 MA=07/09/1993
Lidocaine patch 5% TN= Lidoderm Patch	For relief of allodynia (painful hypersensitivity), and chronic pain in post-herpetic neuralgia.	Hind Health Care, Inc. 3707 Williams Rd., Suite 101 San Jose, CA 95117 DD=10/24/1995 MA= / /
Liothyronine sodium injection TN= Triostat	Treatment of myxedema coma/precoma.	SmithKline Beecham Pharmaceuticals One Franklin Plaza P.O. Box 7929 Philadelphia, PA 19101 DD=07/30/1990 MA=12/31/1991
Lipid/DNA human cystic fibrosis gene TN=	Treatment of cystic fibrosis	Genzyme Corporation P.O Box 9322 One Mountain Road Framingham, MA 01701 DD=04/08/1996 MA= / /
Liposomal Cyclosporin A TN= Cyclospire	For aerosolized administration in the prevention and treatment of lung allograft rejection and pulmonary rejection events associated with bone marrow transplantation.	Vernon Knight, M D Baylor College of Medicine, Dept. of Molecular Physiology One Baylor Plaza Houston, TX 77030 DD=04/30/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of osteosarcoma.	Endorex Corp 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal N-Acetylglucosminyl-N-Acetyl muramly-L-Ala-D-isoGln-L-Al a -gylcerolidpalmitoyl TN= ImmTher	Treatment of Ewing's sarcoma.	Endorex Corp. 900 North Shore Drive Lake Bluff, IL 60044 DD=06/10/1998 MA= / /
Liposomal amphotericin B TN= AmBisome	Treatment of cryptococcal meningitis	Fujisawa USA, Inc 3 Parkway North Center Deerfield, IL 60015 DD=12/10/1996 MA=08/11/1997



To Pharmacist:

This product **MUST** be dispensed in this child-resistant pouch.
Please place all envelopes and the package insert in this child-resistant pouch prior to dispensing and discard the carton.

CHILD-RESISTANT POUCH
9 x 12in

Endo®

Endo Laboratories

July 21, 2000

Re: Lidoderm® (lidocaine patch 5%) Packaging Change

Dear Pharmacist,

The U S Consumer Product Safety Commission (CPSC) has taken the position that Lidoderm® is subject to the Poison Prevention Packaging Act regulations The purpose of this letter is to advise you of a new procedure to follow in dispensing Lidoderm® at the request of the CPSC

Endo Laboratories is developing a new, child-resistant, commercial package for Lidoderm® Until the new packaging is available, we are providing separate child-resistant pouches for use when dispensing Lidoderm®. We are notifying you of this development at this time and ask for your cooperation during the transition

Effective August 1, 2000, this child-resistant pouch will be inside each carton of Lidoderm® shipped to our customers Please call 1-800-462-3636 to receive a complimentary supply of child-resistant pouches to be used to dispense the supply of Lidoderm® that is currently on your shelves.

Until the new package is available, you must dispense Lidoderm® in the child-resistant pouch included in each box of Lidoderm®, unless the customer requests otherwise Each box of Lidoderm® contains six envelopes Whether the prescription calls for one or more envelopes (each envelope contains five individual patches), please place the prescribed amount in the child-resistant pouch and make sure that the pouch is properly closed when you dispense the prescription. For your convenience, we are including instructions for operation of the child-resistant mechanism on the top of each pouch In addition, labels with dispensing instructions have been applied to the lid of each box of Lidoderm® Once the box is empty, please discard it. Additional pouches are available by calling the number listed above

Thank you for your assistance and cooperation We will keep you informed as we progress in the development of the new packaging for Lidoderm® If you have any questions or concerns, please call Endo at 1-800-462-3636

Sincerely,

Matthew Davis, MD, RPh
Director – Medical Affairs

Enclosure Lidoderm® Package Insert

223 WILMINGTON WEST CHESTER PIKE CHADDS FORD PENNSYLVANIA 19317 Tel 610-558-9800

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ATTENTION PHARMACIST:
Child-Resistant Pouch Inside Carton
This product **MUST** be dispensed in the enclosed child-resistant pouch. Please place all envelopes and the package insert in the enclosed child-resistant pouch prior to dispensing and discard the carton.

70615/PF